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SCIENTIFIC ARTICLE

The effect of palonosetron on rocuronium-induced withdrawal movement

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KEYWORDS

Palonosetron;
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movement

Abstract

Background: Rocuronium causes pain and withdrawal movement during induction of anesthesia. In this study, palonosetron was investigated to have analgesic effect on the reduction of rocuronium-induced withdrawal movement.

Methods: 120 patients were randomly assigned to one of three groups to receive either saline, lidocaine 20mg, or palonosetron 0.075mg with a tourniquet applied two minutes before thiopental sodium (5 mg.kg⁻¹) was given intravenously. After loss of consciousness, rocuronium (0.6 mg.kg⁻¹) was injected and the withdrawal movement was estimated by 4-point scale in a double-blind manner.

Results: The overall incidence of rocuronium withdrawal movement was 50% with lidocaine ($p=0.038$), 38% with palonosetron ($p=0.006$) compared with 75% for saline. The incidence of no pain to mild pain was significantly lower in the lidocaine and palonosetron groups (85% and 92% respectively) than in the saline group (58%). However, there was no significant difference in withdrawal movement between the lidocaine and palonosetron groups. There was no severe movement with palonosetron.

Conclusion: Pretreatment of palonosetron with venous occlusion may attenuate rocuronium-induced withdrawal movement as effective as the use of lidocaine. It suggested that peripheral action of palonosetron was effective to reduce rocuronium-induced withdrawal movement.

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PALAVRAS-CHAVE

Palonosetron;
Rocurônio;
Injeção;
Dor;
Movimento de
retirada

O efeito de palonosetron sobre o movimento de retração induzido por rocurônio

Resumo

Justificativa: Rocurônio provoca dor e movimento de retirada durante a indução da anestesia. Neste estudo, avaliamos se palonosetron tem efeito analgésico para reduzir esse movimento induzido por rocurônio.

Métodos: Cento e vinte pacientes foram randomicamente designados para um de três grupos para receber solução salina, lidocaína (20 mg) ou palonosetron (0.075 mg), com aplicação de torniquete dois minutos antes da administração intravenosa de tiopental sódico (5 mg·kg⁻¹). Após a perda de consciência, rocurônio (0.6 mg·kg⁻¹) foi injetado e o movimento de retirada foi avaliado com o uso de uma escala de quatro pontos, de modo duplo-cego.

Resultados: A incidência global do movimento de retirada induzido por rocurônio foi de 50% para lidocaína ($p=0,038$), 38% para palonosetron ($p=0,006$), em comparação com 75% para solução salina. A incidência de dor ausente ou leve foi significativamente menor nos grupos lidocaína e palonosetron (85% e 92%, respectivamente) que no grupo solução salina (58%). Porém, não houve diferença significativa no movimento de retirada entre os grupos lidocaína e palonosetron. Não houve movimento grave com palonosetron.

Conclusão: O pré-tratamento com palonosetron com oclusão venosa pode atenuar o movimento de retirada induzido por rocurônio de modo tão eficaz como o uso de lidocaína. Sugeriu-se que a ação periférica de palonosetron foi eficaz para reduzir o movimento de retirada induzido por rocurônio.

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Introduction

Rocuronium is a commonly used muscle relaxant with a rapid onset and intermediate duration of action. However, rocuronium injection causes withdrawal movements which frequently occur with 50%–80% of incidence.^{1,2} The exact mechanism of rocuronium induced pain is not established but in rare case, it can cause severe complications like aspiration pneumonia.³

Exogenous serotonin 5-Hydroxytryptamine (5-HT) induced neutrophil migration and provoked inflammation and nociception.⁴ Furthermore prostaglandins and dopamine contribute to 5-HT evoked pain.⁵ Pretreatments of 5-HT₃ antagonists in subcutaneous or intrathecal administration significantly reduced 1% formalin induced secondary mechanical allodynia and hyperalgesia in mice. It suggests that peripheral and spinal 5-HT₃ receptor play a role during pain development.⁶ Meanwhile, ondansetron, a 5-hydroxytryptamine-3 (5-HT₃) receptor antagonist, has local anesthetic effect 15 times more potent than lidocaine.⁷ It shows that 5-HT₃ antagonists have analgesic effects through central or peripheral action. Pretreatments with ondansetron, lidocaine, or fentanyl prior to the injection of rocuronium have been used to decrease rocuronium-induced injection pain but showed limited effects on eliminating the pain.² Palonosetron as a 5-HT₃ antagonist recently used for antiemetic, has been reported to be a more potent agent in PONV⁸ and to have a higher affinity of 5-HT₃ receptor among 5-HT₃ antagonists.⁹ Palonosetron 0.075 mg are more effective than 8 mg ondansetron to prevention of PONV.¹⁰

Therefore, palonosetron may have analgesic effect by action on peripheral 5-HT₃ receptor or by local analgesic

property. For attenuation of rocuronium withdrawal movement, we investigated the efficacy of prior administration of lidocaine and palonosetron with applied tourniquet on rocuronium withdrawal movement in laparoscopic surgery.

Methods

One hundred twenty patients aged between 20 and 70 years, belonging to the American Society of Anesthesiologists physical status I or II, who were scheduled for laparoscopic surgery under general anesthesia were recruited into this prospective, randomized, double-blind, controlled study. Patients were excluded if they took any analgesics before operation or had past medical history of cardiac arrhythmia or coronary arterial disease, or had a hypersensitivity reaction to local anesthetics or palonosetron. Written informed consent was obtained after a detailed description of this study, which was approved by the Institutional Review Board of our medical institution.

Patients were randomized into three groups according to study drugs; saline group ($n=40$) with normal saline only, lidocaine group ($n=40$) with lidocaine 20 mg, palonosetron group ($n=40$) with palonosetron 0.075 mg. Each total volume of injection was made up to 3 mL with normal saline prepared by an independent anesthesiologist and the investigators were blinded to drug identity.

No medication was given before surgery. On arrival at the operating room, a 20 gauge intravenous cannula was placed in the dorsum of the non-dominant hand and Ringer's solution was infused at 100 mL/h. Non-invasive blood pressure, pulse oxymeter and electrocardiogram were monitored. After applying a rubber tourniquet applied on the upper

Table 1 Demographic data.

Groups	Saline	Lidocaine	Palonosetron
Age	46.08 ± 13.30	45.72 ± 14.08	46.33 ± 10.96
Sex	14/26	9/31	12/28
Weight	63.92 ± 11.91	61.8 ± 10.48	61.45 ± 11.09
ASA I/II	26/13	22/18	21/19

All values are expressed as means ± SD.

arm to occlude venous drainage, a prepared drug was administered by an investigator who was unaware of the content of the drug. Two minutes after the injection of the drug, the tourniquet was released and 2.5% thiopental sodium 5 mg·kg⁻¹ was administered over 10–15 s. After 20 s, the anesthesiologist checked unconsciousness by verbal response and loss of the eyelash reflex. After loss of consciousness, 1% rocuronium (0.6 mg·kg⁻¹) was injected for 5 s and withdrawal movements were graded by the investigator according to the following scale: 1 – no pain (no response); 2 – mild pain (movement at wrist only); 3 – moderate pain (movement involving the arm only with elbow or shoulder); 4 – severe pain (generalized response or movement in more than one extremity).

We estimated the sample size from a previous pilot study. Withdrawal movement incidence was to occur in 80% of patients following administration of rocuronium,^{11,12} therefore the sample size required for detecting a 30% reduction was 37 patients in each of the 3 groups, at a power of 0.8, an $\alpha = 0.05$. Due to the consideration of dropout cases, sample size was increased to 40 patients per group. Analyses were performed using SPSS 18.0 for Windows (SPSS, Inc., Chicago, IL). Demographic data were analyzed using one-way analysis of variance (ANOVA). Values were expressed as mean ± SD (standard deviation). The incidence of withdrawal movements were analyzed by the χ^2 -test and Fisher's exact test. A *p*-value of <0.05 with Bonferroni correction was considered to be statistically significant.

Results

All 120 patients completed this study. There were no significant differences in the demographic data among the three groups (Table 1).

The grade and incidence of movement withdrawal in each group is shown in Table 2. The overall incidence of rocuronium-induced withdrawal movement was 50% (*p* = 0.038) with lidocaine, 38% (*p* = 0.006) with palonosetron, compared with 75% of saline. There was a significantly lower

incidence of withdrawal movements in patients receiving the lidocaine and palonosetron compared with saline. Whereas the incidence of no or mild pain was significantly higher in lidocaine (85%, *p* = 0.007) and palonosetron group (92%, *p* = 0.001) than in saline group (58%), severe withdrawal movement was significantly higher in the saline than the lidocaine (*p* = 0.0017) and palonosetron (*p* = 0.0003) groups. No patients receiving palonosetron had severe pain. However, there were no significant differences in the incidence of withdrawal movement between lidocaine and palonosetron.

There were no complications such as wheal, inflammation, hematoma, or pain on injection site within 24 h postoperatively.

Discussion

This study demonstrated that palonosetron, a 5-HT₃ antagonist, which is usually used for the prevention of PONV, reduced rocuronium-induced withdrawal movement from 72% in the saline group to 42% in the palonosetron group. The no pain to mild pain associated with rocuronium withdrawal movement was significantly higher in the palonosetron and lidocaine groups compared with the saline group. No patient in the palonosetron group showed severe rocuronium withdrawal movement.

The exact mechanism of rocuronium-induced pain has not been established. The low pH or osmolarity of rocuronium may be associated with the cause of pain,^{13,14} but some reports that osmolarity and pH were not the major cause of rocuronium-induced injection pain exist.^{15,16} Other mechanism may be involved in the activation of nociceptors by kinin cascade, which is similar to the mechanism of propofol evoked pain.¹⁷ The characteristic rocuronium injection pain which patients described was a burning sensation of short duration¹⁸ which caused the movement during rocuronium injection.¹⁶ In an in vivo study, intradermal stimulation with high concentrations of rocuronium revealed significant increases in histamine and tryptase release and led to bursting discharge for 20–40 s of C-fiber.¹⁹ Therefore, rocuronium stimulates C-fiber directly.

Various methods have been proposed for the prevention of rocuronium induced pain. Ketamine, lidocaine opioids and acetaminophen^{12,20–22} were used for pretreatment to reduce pain. Pretreatment with 30–50 mg of lidocaine with a tourniquet applied was more effective than pretreatment with other drugs such as ondansetron, fentanyl, remifentanyl, acetaminophen.^{2,11,22}

Table 2 Incidence and intensity score of withdrawal movements.

Group	Withdrawal movement score				Overall incidence
	1 – no pain	2 – mild pain	3 – moderate pain	4 – severe pain	
Saline	11 (28%)	12 (30%)	6 (15%)	11 (27%)	29 (75%)
Lidocaine	20 (50%) ^a	14 (35%)	5 (13%)	1 (2%) ^a	20 (50%)
Palonosetron	23 (58%) ^a	14 (35%)	3 (7%)	0 (0%) ^a	17 (38%)

Values are presented as numbers of patients (percentages).

^a *p* < 0.05 vs. compared with group saline.

Ondansetron is a 5-hydroxytryptamine-3 antagonist used as an anti-emetic. It acts as a local anesthetic drug by blocking sodium channels in neurons of rat brain. According to this report, ondansetron is 15 times more potent than lidocaine as a local anesthetic.⁷ Ondansetron acts as an opioid u receptor agonist.²³ 5-HT caused pain after injection on the hindpaw of rats. Furthermore 5-HT produced an increase in neutrophil activity, local release of prostaglandins and dopamine. Released dopamine contributes to 5-HT mediated nociception.⁵ Zeltz et al.²⁴ indicated that 5-HT₃ receptor is expressed not only by primary afferent fiber but also by thinly myelinated fiber and C-fibers. In addition, serotonin contributes to pain development by activation of small diameter peripheral afferents and release of proinflammatory peptides such as substance P. In humans, 5-HT injected into the masseter muscle elicits pain and allodynia/hyperalgesia.²⁵ Therefore, 5-HT₃ antagonists including ondansetron, palonosetron, may have analgesic properties by acting as peripheral 5-HT receptor antagonists, sodium channel blockers, or opioid agonists.

In general, 4mg of ondansetron is administrated with venous occlusion to reduce the injection pain of rocuronium or propofol.^{2,26} It suggested that the peripheral action of ondansetron reduced rocuronium withdrawal movement. Cho et al.²⁷ reported that palonosetron with systemic administration reduced rocuronium withdrawal movement. But intravenous injection of palonosetron without venous occlusion could not reveal the exact action site whether peripherally or centrally. In our study, palonosetron was administrated with a tourniquet applied and not only showed a significant analgesic effect when compared with saline but also showed an effect similar to that of 20 mg lidocaine on rocuronium withdrawal movement. Therefore, we showed that palonosetron reduces withdrawal movement of rocuronium with venous occlusion via peripheral action.

Palonosetron has a long half-life compared to other 5-HT₃²⁸ and is usually injected prior to anesthetic induction for prevention of early and late PONV.²⁹ Therefore, pretreatment with palonosetron prior to induction has meaning for prevention of PONV and for reducing rocuronium induced withdrawal movement.

The limitation of our research was we could not reveal the exact analgesic mechanism of palonosetron by peripheral 5-HT₃ receptor, sodium channel or u opioid receptor. Further research will be needed to determine the kinds of receptors involved in reducing rocuronium withdrawal movement.

In conclusion, we demonstrated that palonosetron is an effective analgesic for the reduction of rocuronium withdrawal movement similar to a small dose of lidocaine with tourniquet applied.

Conflicts of interest

The authors declare no conflicts of interest.

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